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Linda S. Cook  
PI - Signature

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Date

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## **Introduction**

This proposal provides funding for two years of postdoctoral training to support Dr. Cook's work on analyses involving the epidemiology of breast cancer in women. These analyses are being conducted using data from three population-based case control studies that collected detailed information on many factors known, or suspected to be, related to the risk of breast cancer. These analyses evaluate hypotheses of scientific and public health interest that were not identified as specific aims in the original grant protocols. The proposed analyses explore the relationship between various reproductive, lifestyle, and occupational exposures and breast cancer risk for which inconsistent or inconclusive associations have been reported. Briefly, we have evaluated if personal use of hair dye among young women is associated with an increased risk of breast cancer. We are in the process of evaluating whether a recent term pregnancy results in a transient increase in breast cancer risk, and whether various aspects of lactation are associated with a decrease in breast cancer risk. Later in the coming year (1997-1998), we will explore different types and groupings of occupations, and presumed exposure to electromagnetic fields and strenuous physical activity, to assess the influence of occupation on the risk of breast cancer.

## **Progress Report**

The purpose, contribution, and status of each analysis is indicated below.

### **1. Hair dye use:**

The purpose of this analysis was to evaluate whether or not hair dye use increases breast cancer risk among young women. The results of this analysis were presented at the 30th annual meeting of the Society for Epidemiologic Research (SER) in Edmonton, Alberta (June 1997). We are still preparing the final manuscript to submit for publication in a peer-reviewed journal; thus, to honor journal related embargoes, the following includes the results and discussion as presented at the SER meeting.

#### Introduction

The reported mutagenic effects of permanent and semi-permanent hair dyes (1) and the carcinogenic effects of some coal-tar derivatives found in hair coloring products (2), has raised concern that personal hair dye use could increase the risk of breast cancer. Early studies that explored this possibility found some modest increases in risk, particularly among subgroups of women (e.g. those with long durations of regular use or among smokers only) (3-8). Later studies found no over-all association with permanent hair dye use or the duration of use (9-14). However, the majority of women in the later studies were 50 years of age or older. In this population-based case control study, information on the type, duration, and frequency of hair coloring application was collected to evaluate the impact of hair coloring on the risk of breast cancer among reproductive-age women.

#### Methods

Eligible case women included white women residing in three counties of western Washington who were diagnosed with insitu or invasive breast cancer between 1983 and 1990 and who were born in 1945 or later. Thus, all case women were 21-45 years of age. These women were identified through the Cancer Surveillance System of western Washington, a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. After obtaining written, informed consent, 83.6% of the eligible case women were successfully interviewed. We excluded one woman with unknown hair coloring application, leaving 844 women available for analysis (n=97 in-situ and n=747 invasive cases).

Women of similar age, who lived in these counties and were identified by random digit dialing, served as controls. 97% of residences were successfully screened and after obtaining written, informed consent, 78.0% of eligible control women were successfully interviewed. We excluded one woman with unknown hair coloring application, leaving 960 control women for analysis.

The women completed a structured, in-person interview and provided information on demographic and lifestyle characteristics, as well as reproductive and medical histories. Additionally, women were queried about hair coloring application. Those who answered affirmatively were further questioned about their natural hair color, the types of hair coloring used, the desired color results, the frequency of application, and the amount of time the coloring product remained on their hair to achieve the desired result. Types of hair coloring were recorded under five categories: rinses (coloring applied to hair that washed out the next

shampoo), semi-permanent dyes (coloring that remained over multiple washings), permanent dyes (coloring never washed out), bleaching then dyeing with either semi-permanent or permanent dyes, or frosting/tipping (partial coloring of hair). In the present analysis semi-permanent and permanent dye use was combined since the results for each analysis separately were very similar. Women were also queried about using hair spray, and for those that used hair spray, the frequency of use. Information on hair spray use was available for 770 (91.2%) of the 844 breast cancer cases and all control women.

### Results

Apart from hair coloring application, the distribution of other characteristics of our cases and controls was consistent with the known or suspected factors influencing breast cancer risk among young women. For example, cases women were slightly more likely to be nulliparous than control women and much more likely to have a family history of breast cancer in a first degree relative. These characteristics along with weight were also related to hair coloring application. All odds ratios presented in this analysis are adjusted for age, parity, weight, and a family history of breast cancer in a first degree relative. Further adjustment for education, income, religious affiliation, marital status, height, oral contraceptive use, age at menarche, age at first fullterm birth, or smoking and alcohol consumption did not alter the estimated odds ratios.

For all the relative risk estimates reported in the present analysis, women who reported any method, type, or frequency of hair coloring application were compared to women who stated they had never colored their hair - a group consisting of 315 breast cancer cases and 418 controls. Slightly more cases than controls, 62.7% vs. 56.5% respectively, reported some type hair color application, resulting in a small elevation in the risk for breast cancer (Table 1). However, there was no increasing risk with increased frequency of use, illustrated here by the total lifetime episodes of hair coloring application, and no elevation in risk for the large number of women who had colored their hair within 4 years of reference date.

Table 1. Hair coloring application and the risk of breast cancer.

	Cases ( n )	Controls ( n )	Adjusted OR*	(95% CI)
<b>Use of hair coloring :</b>				
none	315	418	1.00	referent
any	529	542	1.28	(1.05, 1.56)
<b>Total lifetime episodes:</b>				
1 - 2	108	126	1.23	(0.91, 1.67)
3 - 9	130	142	1.21	(0.90, 1.62)
10 - 34	140	132	1.40	(1.05, 1.88)
$\geq 35$	140	138	1.29	(0.97, 1.73)
<b>Time since last use:</b>				
$\leq 4$ yrs	304	330	1.19	(0.95, 1.49)
5 - 14 yrs	123	105	1.64	(1.21, 2.24)
$\geq 15$ yrs	101	106	1.20	(0.86, 1.65)

\* adjusted for age, parity, weight in kilograms, and a family history of breast cancer.

Table 2. Breast cancer risk by specific types of hair coloring use.

	Cases (n)	Controls (n)	Adjusted OR*	(95% CI)
<b>Use of hair coloring :</b>				
none	315	418	1.00	referent
Any rinses	92	66	1.72	(1.19, 2.49)
Only rinses	23	18	1.69	(0.88, 3.26)
Any semi-permanent/permanent	406	424	1.27	(1.02, 1.56)
Only semi-permanent/permanent	254	316	1.06	(0.84, 1.34)
Any bleach then dye	69	39	2.54	(1.64, 3.94)
Only bleach then dye	7	7	1.49	(0.49, 4.47)
Any frosting/tipping	194	167	1.55	(1.19, 2.02)
Only frosting/tipping	63	74	1.15	(0.79, 1.68)

\* adjusted for age, parity, weight in kilograms, and a family history of breast cancer.

Table 3. Hair spray use and the risk of breast cancer.

	Cases (n=770)	Controls (n=960)	Adjusted OR*	(95% CI)
<b>Hair spray use:</b>				
none	126	161	1.00	referent
any	640	795	0.99	(0.76, 1.29)
<b>Total lifetime episodes:</b>				
< 400	124	154	1.13	(0.80, 1.60)
401 - 2000	134	187	0.94	(0.67, 1.31)
2001 - 6000	161	236	0.85	(0.62, 1.17)
> 6000	218	215	1.10	(0.80, 1.52)

\* adjusted for age, parity, weight in kilograms, and a family history of breast cancer.

Because many women used more than one method of hair coloring application, breast cancer risk was further assessed for those that exclusively used one of the four methods of application and for those that reported any use of the four methods of application (Table 2). Among the small number of women who reported exclusive use of rinses there was a

suggestion of an elevated risk, but the confidence interval is wide and includes the null value. Among those with exclusive use of semi-permanent and/or permanent dyes or exclusive frosting or tipping application there was no elevation in breast cancer risk. The risk for those women who reported first bleaching and then dyeing their hair is not clear since only 7 cases and 7 controls reported this exposure.

We found modest elevations in breast cancer risk for those who reported any use of the four methods of hair coloring application. However, no one type of hair coloring application (for example rinses or frosting) in combination with the other types appeared to account for the elevation in risk (data not shown). Furthermore, we found no increasing risk with increased frequency of use or any consistent pattern of risk associated with the timing of use (data not shown).

Any hair spray use and the total number of times it was applied to hair was not related to the risk of breast cancer (Table 3). This was also true when we examined aerosol sprays and pump sprays separately (data not shown).

### Discussion

While our results suggests that the impact, if any, of hair coloring application on breast cancer risk is small, there are several issues that should be considered in the interpretation of our results. Eighty-four percent of eligible cases and 76% of eligible controls participated in our study. If substantial differences in hair color application existed between participating and non-participating women, our study results may over- or under-estimate the true risks for breast cancer.

Additionally, it is not clear how well summary measures of hair color application correctly estimate actual exposure to any particular constituent(s) in these products that may influence breast cancer risk. Women in the present study colored their hair over a period of time from 1953 through 1990, with over 95% of use occurring between 1960 and 1990. The hair coloring formulations changed over this time period and products were also introduced and removed from the consumer market during this time period.

It is also possible that the completeness of the reporting of hair coloring application differed between cases and controls, biasing our relative risk estimates to some degree.

While we found a small elevation in breast cancer risk associated with any use of hair coloring, exclusive use of one of the four types of hair coloring application was not associated with elevated risks for breast cancer among reproductive-age women. It is not clear why we found an elevated breast cancer risk associated with any use of one of the four types of hair coloring application. Elevations in risk were not restricted to one type of hair coloring application (for example rinses or frosting) in combination with the other types. Furthermore, we found no increasing risk with increased frequency of use or any consistent pattern of risk associated with the timing of use. And finally, hair spray use was not associated with an elevation in breast cancer risk.

The results of other studies that have investigated the impact of hair coloring application on breast cancer risk that specifically reported risks for reproductive-age women have been inconsistent; one reported an elevated risk (6), one a suggestion of an elevated risk (11), and one no elevation in risk (10). In our study, the lack of an association between exclusive use of a single type of hair coloring application and breast cancer risk, particularly among the large number of women who exclusively used semi-permanent and permanent dyes, argues

that hair coloring application does not influence breast cancer risk among reproductive-age women. However, we did see a small elevation in breast cancer risk associated with the use of any hair coloring. Thus, we cannot preclude the possibility that there may be a small elevation in breast cancer risk associated with hair coloring application.

If the potential small increased risk for breast cancer is investigated further, the uncertainty associated with reported hair coloring exposures needs to be reduced. Cohort studies with detailed cumulative lifetime exposures would remove subject recall errors and still be able to evaluate details of hair coloring application. Furthermore, toxicological studies of the absorption, metabolisms, and carcinogenic potential of constituents and mixtures of constituents in hair coloring products are needed to establish possible mechanisms of carcinogenesis.

## 2. Recent term pregnancy

The purpose of this analysis is evaluate whether a term pregnancy increases the risk of breast cancer for some period of time following that pregnancy. We have an analysis approach which we believe will allow a more meaningful estimation of the short- and long-term impact of having one more child on the risk of breast cancer than has been utilized in prior studies. Results of this analysis will be presented at the Era of Hope meeting of the Department of Defense Breast Cancer Research Program in Washington DC (Oct/Nov 1997). This particular analysis is a combined analysis of two case-control studies. Just recently (June 15, 1997), we received the data from one of the case-control studies. Thus, the abstract submitted for the Era of Hope meeting was a preliminary analysis based on one of the case-control studies. The final analysis using both studies is currently in progress. The following is a copy of the extended abstract submitted for the 1997 Era of Hope meeting.

A term pregnancy, especially early in reproductive life, has consistently been associated with a reduced risk of breast cancer. However, there is some evidence suggesting that for reproductive-age women a term pregnancy confers either no change in risk, or actually increases the risk of breast cancer for some period of time following that pregnancy episode. Evaluation of breast cancer risk by the time since the last birth can be approached in two ways, depending on the study question. To assess the impact of the last birth occurring earlier or later in life, breast cancer risk can be evaluated by the recency of the last birth among multiparous women. To assess the impact of an additional birth, breast cancer risk can be evaluated by comparing women of any given parity to comparable women with one less term pregnancy. In the present case-control study, we used both approaches to address the risk of breast cancer by the time since last birth.

Breast cancer cases included all women aged 21-45 diagnosed with in-situ or invasive breast cancer between January 1, 1983 and April 30, 1990 in three metropolitan counties covered by the population-based cancer registry of western Washington (n=845). A sample of women of similar age and residence who were identified by random digit dialing serve as controls (n=960). Information on pregnancies and other reproductive factors, as well as information on other potential risk factors, was ascertained during an in-person interview. (When available, approximately 170 women aged 21-45 diagnosed with breast cancer between November 1, 1992 and April 31, 1995, and approximately 170 control women of similar age and county of residence, will be added to the study population.)

In this preliminary analysis, we evaluated the impact of the last birth occurring earlier or later in life by comparing the time since the last birth among multiparous women (n=486 case women and n=494 control women) using 10 or more years as the reference category. After adjustment for age, parity, age at first birth, and a family history of breast cancer in a first degree relative, the relative risk (RR) of breast cancer varied little by the time since the last birth: for less than 3 years, RR=0.97 (95% confidence interval [CI]=0.58, 1.61); for 3 to 6 years, RR=0.94 (95% CI=0.63, 1.40); for 7 to 9 years, RR=0.94 (95% CI=0.63, 1.40). The lack of association was also present in subgroups of women defined on the basis of age or a history of breast feeding with the last childbirth.

We also evaluated the impact of an additional birth by comparing the time since last birth among women of any given parity to comparable women with one less childbirth. Thus, women of parity 4 were compared to women of parity 3, women of parity 3 were compared to women of parity 2, etc. These comparisons were made separately for three age groups of women (21-35, 36-40, 41-45) while adjusting for a family history of breast cancer in a first degree relative and age at first childbirth. There was no clear pattern of an increased breast cancer risk for women who had one more child. For example, among women aged 36 to 40 years, the relative risks for breast cancer by the time since the last birth for women who had two children relative to women who had one were 0.59 (95% CI=0.33, 1.06), 0.74 (95% CI=0.45, 1.21), and 0.78 (95% CI=0.50, 1.23) if the birth occurred in the previous 5 years, 5 to 9 years, or 10 or more years, respectively. Analogous relative risks for women who had three children compared to those with two were 1.08 (95% CI=0.56, 2.08), 1.77 (95% CI=0.93, 3.35), and 1.32 (95% CI=0.73, 2.36).

To date, our results do not support an increased risk of breast cancer during a period of several years following a pregnancy or among women who had a term pregnancy that occurred relatively late in their reproductive life.

### 3. Lactation

The purpose of this analysis is to evaluate whether or not lactation results in a decreased risk of breast cancer; and if so, the particular aspect of breast feeding that confers the protection. At present, the impact of lactation on breast cancer risk is unclear. In our large population of women (20 to 74 years of age) we will have the power to assess risk in relation to the total duration, mean duration, and recency of breast feeding. We will also be able to investigate breast cancer risk in relation to aspects of lactation that have received little attention, such as the reasons for not breast feeding, reasons for stopping breast feeding, use of lactation suppressants, and favoring one breast over the other while breast feeding. This particular analysis is a combined analysis of three case-control studies. Just recently (June 15, 1997), we received the data from one of the case-control studies. Since we are currently in the process of combining the datasets and creating summary variables for analysis, there are no preliminary analyses to date.

### 4. Occupation

The purpose of this analysis is to investigate the influence of occupational history on breast cancer risk. Our evaluation of the impact of occupations and groups of occupations on breast cancer risk in young women (<45 years of age) may be particularly informative due to their expected high prevalence of employment outside the home. In particular, we will assess the impact of occupational exposure to strenuous physical activity and high levels of electromagnetic

fields among both young (<45 years of age) and middle-aged women (50 to 64 years of age). This analysis has just been initiated with the creation of a raw data file with reported job title, industry, and years worked. The next phase of this analysis involves consulting with an occupational epidemiologist / industrial hygienist (Dr. Paul Demers, University of British Columbia) who will review all occupation and industry responses, blinded to case-control status, in order to categorize responses according to their likely level of physical activity by rating job titles and industries according to criteria used by the U.S. Department of Labor. Since this analysis has just been initiated, there are no preliminary analyses to date.

## **Conclusions**

Of the four analyses funded by the U.S. Army Medical Research and Materiel Command under DAMD-14-96-1-6118, one has been completed, two are in progress, and one has just been initiated. To date, no conclusions can be drawn from the latter three analyses.

In the completed analysis, we found a small elevation in breast cancer risk associated with any use of hair coloring; however, exclusive use of one of the four types of hair coloring application was not associated with elevated risks for breast cancer among reproductive-age women. It is not clear why we found an elevated breast cancer risk associated with any use of one of the four types of hair coloring application. Elevations in risk were not restricted to one type of hair coloring application (for example rinses or frosting) in combination with the other types. Furthermore, we found no increasing risk with increased frequency of use or any consistent pattern of risk associated with the timing of use. And finally, hair spray use was not associated with an elevation in breast cancer risk.

The results of other studies that have investigated the impact of hair coloring application on breast cancer risk that specifically reported risks for reproductive-age women have been inconsistent; one reported an elevated risk, one a suggestion of an elevated risk, and one no elevation in risk. In our study, the lack of an association between exclusive use of a single type of hair coloring application and breast cancer risk, particularly among the large number of women who exclusively used semi-permanent and permanent dyes, argues that hair coloring application does not influence breast cancer risk among reproductive-age women. However, we did see a small elevation in breast cancer risk associated with the use of any hair coloring. Thus, we cannot preclude the possibility that there may be a small elevation in breast cancer risk associated with hair coloring application.

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